M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
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FROM: David G. Orloff, M.D.
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TO: NDA 21-865
Pargluva (muraglitazar) Tablets
Treatment of type 2 diabetes mellitus

SUBJECT: Background and summary of issues for discussion at Advisory Committee meeting on September 9, 2005

Background

Muraglitazar is a dual (gamma, alpha) non-thiazolidinedione PPAR agonist proposed for the treatment of type 2 diabetes mellitus. It shares pharmacologic mechanisms with the two approved PPAR gamma agonists (rosiglitazone and pioglitazone) and with the fibric acid derivatives, including gemfibrozil and fenofibrate. As such, by design and as demonstrated in clinical studies, it has apparent salutary effects on both glucose and lipid metabolism.

The pharmacology and preclinical (animal) toxicology of muraglitazar and of a large number of gamma and dual PPAR agonists also under development continue under extensive review by Dr. El Hage and her staff. Dr. El Hage will discuss selected, relevant preclinical toxicologic findings with muraglitazar in the context of the overall "class" findings. Additionally, the rodent carcinogenicity of this heterogeneous class of drugs is a subject of obvious intensive study by pharmaceutical sponsors and by the FDA. Dr. El Hage will also present an overview of the state of knowledge in that regard, obviously with specific reference to the findings with muraglitazar.

The clinical safety and efficacy of rosiglitazone and pioglitazone have been extensively evaluated both pre-approval (both were approved in 1999) and post-approval. Most notable from a clinical safety standpoint is that both drugs are associated with dose-related fluid retention, manifest as weight gain (which is compounded by the PPAR gamma-mediated adipose tissue proliferation), edema, and congestive heart failure. These effects on fluid balance appear to "track" with the glucose lowering effects of these drugs; indeed, it is well recognized that the use of these agents in combination regimens with insulin, while resulting in overall improved control of glucose relative to either monotherapy, is fraught with clear increased risk of marked fluid retention and presumed unmasking of previously subclinical cardiac functional compromise. It is furthermore apparent that for any degree of response with respect to glycemic control, there is a spectrum of susceptibility to the fluid retaining effects of PPAR gamma agonists. Data from the muraglitazar trials show that this drug shares these presumed PPAR gamma-mediated clinical effects. Insofar as the glucose-lowering effects of muraglitazar 5 mg exceeded those of pioglitazone 30 mg in the clinical comparisons undertaken by BMS investigators, so too did the

fluid-overload-related cardiovascular side effects of muraglitazar 5 mg exceed those of pioglitazone 30 mg. Finally, although a subject of great clinical interest and ongoing investigation, the effects of PPAR gamma agonists on modifying cardiovascular risk in patients with type 2 diabetes have not been established. The cardiovascular safety of muraglitazar is a central issue for discussion by the advisory committee.

Principal objectives of the Pargluva program

The sponsor, through extensive clinical investigations, has established the efficacy of Pargluva in the control of glycemia in patients with type 2 diabetes as monotherapy, as well as in combination with metformin or sulfonylurea. The mean absolute (not placebo-subtracted) HbA1c reductions with the proposed doses of 2.5 and 5 mg muraglitazar daily ranged from 0.9 to 1.2 percentage units. Additionally, at these doses, muraglitazar was associated with consistent average reductions in triglycerides, apo B, and non-HDL-cholesterol, and with mean increases in HDL-C across the submitted trials.

The clinical safety of muraglitazar has been addressed in phase 2 and 3 studies in which approximately 3200 patients were exposed to various doses of drug, including some 2700 patients treated for up to 2 years. Over 1100 patients were exposed for greater than 36 weeks to the proposed doses of 2.5 and 5 mg daily. The study population appears representative of the general population with type 2 diabetes, with regard to duration and severity of disease, and clearly included patients at very high risk for cardiovascular disease events, as is evident from review of the narrative histories of some of the patients who experienced CVD events on treatment.

Central issues

The efficacy of the proposed 2.5 and 5 mg daily muraglitazar doses is clear. That said, the clinical and statistical reviews of efficacy raise the issue that the 1.5 mg dose of muraglitazar, though not proposed for marketing by the sponsor in the U.S., appears effective. Based on the *in vitro* pharmacology of the drug and confirmed in the animal toxicology studies of muraglitazar, it is apparent that the PPAR gamma effects of the drug predominate over alpha effects at clinical exposures. Based on the known efficacy of certain other oral hypoglycemic agents, it is arguable that clinically significant gamma effects (i.e., glucose control) are achieved at doses of muraglitazar below 2.5 mg. On the other hand, eliciting the alpha effects of muraglitazar may well require doses associated with adverse gamma effects in susceptible individuals.

As above, muraglitazar, like other PPAR gamma agonists, was found to cause fluid accumulation and as such to precipitate congestive heart failure in susceptible individuals. This is particularly evident with the high doses (10 mg and 20 mg daily) studied but not proposed for marketing. In addition, though, the 5 mg dose, which appeared marginally more potent for glucose lowering than 30 mg of pioglitazone in head-to-head comparisons, was also associated with higher rates of fluid-related adverse events.

An imbalance in the incidences of cardiovascular deaths and of serious cardiovascular adverse events (other than CHF) relative to placebo and pioglitazone has arisen in the muraglitazar clinical trial experience. These differences are based on very small numbers of events in individual studies and on small numbers overall. Furthermore, they are primarily driven by the

outcomes in two of the many trials submitted (i.e., one trial drives the death imbalance; another trial drives the non-CHF cardiovascular adverse events imbalance) in patients who had failed either metformin or sulfonylurea therapy, and thus may represent groups at higher risk for CVD. The extent to which the known and expected effect of this potent PPAR gamma to cause fluid retention might have contributed to the overall observed imbalance must be considered. In other words, if any events were caused or contributed to by drug, a central question is whether these were the adverse consequences of the fluid effects of a PPAR gamma (the cases of CV death were all at 5 mg or above), or whether some other, unexpected pharmacologic effect was manifest. In that vein, the pharmacology of the drug and the preclinical findings with muraglitazar suggest neither arrhythmogenic nor thrombotic effects, nor a direct cardiac or vascular toxic potential in humans.

Complicating any evaluation of possible causation by drug is the fact that cardiovascular (particularly atherosclerotic) events are common in patients with type 2 diabetes (and review of the case narratives makes clear that the affected patients were at very high baseline risk—see the Appendix in Dr. Golden's review). Furthermore, imbalances across randomized treatment groups in level of cardiovascular risk as a function of a multitude of risk factors and possible contributory influences (e.g., other medications) are possible, but even if such imbalances could be enumerated, it is extremely difficult to implicate any or all *post hoc* as explaining observed differences in the incidence of clinical events. In short, establishing a role of study drug in individual cases of cardiovascular adverse events or death is exceedingly difficult, yet so too is eliminating the study drug, case by case, as a potential contributor to the event. A careful review of individual cases in order to inform discussion and conclusions about likely causation by muraglitazar has been undertaken by Dr. Golden.

Finally, the universal (though varied) rodent carcinogenicity of PPAR agonists generally, apparently receptor-mediated (these compounds are not genotoxic in standard assays) has raised questions and concerns about carcinogenic risk in humans. This will be discussed by Dr. El Hage.

We look forward to a fruitful discussion of this application on September 9.

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